



# TREATMENT WITH FERMENTED MISTLETOE (*VISCUM ALBUM L.*) EXTRACT AS PART OF LONG-TERM SUPPORTIVE CARE IN PATIENTS WITH PRIMARY NON-METASTATIC COLORECTAL CARCINOMA

W.E. Friedel<sup>1</sup> MD, H. Matthes<sup>2</sup> MD, P. Heusser<sup>3</sup> MD, MME, P.R. Bock<sup>4</sup> MD

<sup>1</sup> Hospital Bad Bocklet, Dept. Internal Medicine and Oncology, Bad Bocklet, Germany; <sup>2</sup> Hospital Havelhöhe, Dept. Oncology, Berlin, Germany; <sup>3</sup> Inst. of Complementary Medicine KIKOM, University of Bern, Switzerland; <sup>4</sup> Inst. for Applied Medical Research, IFAG Basel, Switzerland

Gemeinschaftskrankenhaus  
Havelhöhe  
Klinik für onkologisch erweiterte Heilkunst



## SUMMARY

The treatment with the fermented mistletoe extract Iscador® (ISC) was evaluated as part of supportive care of surgically treated patients with primary non-metastatic colorectal carcinoma (UICC stage I-III) in comparison with a parallel control group without ISC in a multicenter, epidemiological, observational cohort study in Germany and Switzerland. ISC was given in addition to conventional adjuvant chemo- and/or radiotherapy or passive aftercare, while the control group was treated with conventional therapy or passive aftercare without ISC. In 804 (429 ISC and 375 control) evaluable patients from 26 centers, the majority of the baseline characteristics, prognostic criteria, and therapy was sufficiently balanced between the therapy groups. After a median follow up of 58 vs. 51 months, and a median ISC therapy duration of 52 months, the ISC-group showed significantly fewer ADRs attributed to the conventional therapy, fewer persistent disease and therapy related symptoms, better functional condition, shorter need for hospitalization, and longer disease-free survival than the parallel control group without ISC therapy. ISC treatment was well tolerated and showed a beneficial role in the supportive care in primary non-metastatic colorectal carcinoma.

## PATIENTS

In a total of 804 evaluable patients (429 ISC and 375 control) from 26 centers, the majority of the baseline characteristics, prognostic criteria, and main therapeutic measures was sufficiently balanced between the groups. The median follow-up time was 58 (ISC) vs. 51 months (control), the median therapy duration 52 months. All patients were surgically treated. The baseline demographic and prognostic factors are summarized in Table 1 and the treatment regimen is presented in Table 2.

| Characteristic               | ISC-group<br>(n=429) | Control<br>Group<br>(n=375) |
|------------------------------|----------------------|-----------------------------|
| Age, mean (SD), years        | 55.1 (11.1)          | 54.4 (11.1)                 |
| Sex, %                       |                      |                             |
| Male                         | 49.9                 | 46.7                        |
| Female                       | 50.1                 | 53.3                        |
| Location, %                  |                      |                             |
| Cecum                        | 19.9                 | 19.4                        |
| Ascending                    | 30.2                 | 30.2                        |
| Transverse                   | 19.9                 | 19.9                        |
| Descending                   | 18.8                 | 18.8                        |
| Sigmoid                      | 11.2                 | 11.2                        |
| Rectum                       | 8.9                  | 8.9                         |
| Tumor stage pT, %            |                      |                             |
| T1 (1.2-2.4 cm)              | 4.1                  | 2.2                         |
| T2 (2.5-4 cm)                | 19.9                 | 18.2                        |
| T3 (4.1-5 cm)                | 21.5                 | 19.5                        |
| T4 (5.1-10 cm)               | 54.5                 | 60.1                        |
| Tumor stage pN, %            |                      |                             |
| N0 (no lymph nodes)          | 18.2                 | 19.9                        |
| N1 (1-3 lymph nodes)         | 19.9                 | 19.9                        |
| N2 (4-10 lymph nodes)        | 58.2                 | 58.2                        |
| N3 (>10 lymph nodes)         | 11.9                 | 11.9                        |
| Tumor stage UICC, %          |                      |                             |
| I/II                         | 10.4                 | 10.4                        |
| III                          | 11.2                 | 11.2                        |
| IV                           | 78.4                 | 78.4                        |
| Tumor status post-surgery, % |                      |                             |
| R0                           | 92.2                 | 90.2                        |
| R1                           | 7.8                  | 9.8                         |
| R2                           | 0                    | 0                           |
| R3                           | 0                    | 0                           |
| R4                           | 0                    | 0                           |
| R5                           | 0                    | 0                           |
| R6                           | 0                    | 0                           |
| R7                           | 0                    | 0                           |
| R8                           | 0                    | 0                           |
| R9                           | 0                    | 0                           |
| R10                          | 0                    | 0                           |
| R11                          | 0                    | 0                           |
| R12                          | 0                    | 0                           |
| R13                          | 0                    | 0                           |
| R14                          | 0                    | 0                           |
| R15                          | 0                    | 0                           |
| R16                          | 0                    | 0                           |
| R17                          | 0                    | 0                           |
| R18                          | 0                    | 0                           |
| R19                          | 0                    | 0                           |
| R20                          | 0                    | 0                           |
| R21                          | 0                    | 0                           |
| R22                          | 0                    | 0                           |
| R23                          | 0                    | 0                           |
| R24                          | 0                    | 0                           |
| R25                          | 0                    | 0                           |
| R26                          | 0                    | 0                           |
| R27                          | 0                    | 0                           |
| R28                          | 0                    | 0                           |
| R29                          | 0                    | 0                           |
| R30                          | 0                    | 0                           |
| R31                          | 0                    | 0                           |
| R32                          | 0                    | 0                           |
| R33                          | 0                    | 0                           |
| R34                          | 0                    | 0                           |
| R35                          | 0                    | 0                           |
| R36                          | 0                    | 0                           |
| R37                          | 0                    | 0                           |
| R38                          | 0                    | 0                           |
| R39                          | 0                    | 0                           |
| R40                          | 0                    | 0                           |
| R41                          | 0                    | 0                           |
| R42                          | 0                    | 0                           |
| R43                          | 0                    | 0                           |
| R44                          | 0                    | 0                           |
| R45                          | 0                    | 0                           |
| R46                          | 0                    | 0                           |
| R47                          | 0                    | 0                           |
| R48                          | 0                    | 0                           |
| R49                          | 0                    | 0                           |
| R50                          | 0                    | 0                           |
| R51                          | 0                    | 0                           |
| R52                          | 0                    | 0                           |
| R53                          | 0                    | 0                           |
| R54                          | 0                    | 0                           |
| R55                          | 0                    | 0                           |
| R56                          | 0                    | 0                           |
| R57                          | 0                    | 0                           |
| R58                          | 0                    | 0                           |
| R59                          | 0                    | 0                           |
| R60                          | 0                    | 0                           |
| R61                          | 0                    | 0                           |
| R62                          | 0                    | 0                           |
| R63                          | 0                    | 0                           |
| R64                          | 0                    | 0                           |
| R65                          | 0                    | 0                           |
| R66                          | 0                    | 0                           |
| R67                          | 0                    | 0                           |
| R68                          | 0                    | 0                           |
| R69                          | 0                    | 0                           |
| R70                          | 0                    | 0                           |
| R71                          | 0                    | 0                           |
| R72                          | 0                    | 0                           |
| R73                          | 0                    | 0                           |
| R74                          | 0                    | 0                           |
| R75                          | 0                    | 0                           |
| R76                          | 0                    | 0                           |
| R77                          | 0                    | 0                           |
| R78                          | 0                    | 0                           |
| R79                          | 0                    | 0                           |
| R80                          | 0                    | 0                           |
| R81                          | 0                    | 0                           |
| R82                          | 0                    | 0                           |
| R83                          | 0                    | 0                           |
| R84                          | 0                    | 0                           |
| R85                          | 0                    | 0                           |
| R86                          | 0                    | 0                           |
| R87                          | 0                    | 0                           |
| R88                          | 0                    | 0                           |
| R89                          | 0                    | 0                           |
| R90                          | 0                    | 0                           |
| R91                          | 0                    | 0                           |
| R92                          | 0                    | 0                           |
| R93                          | 0                    | 0                           |
| R94                          | 0                    | 0                           |
| R95                          | 0                    | 0                           |
| R96                          | 0                    | 0                           |
| R97                          | 0                    | 0                           |
| R98                          | 0                    | 0                           |
| R99                          | 0                    | 0                           |
| R100                         | 0                    | 0                           |

Table 1: Baseline characteristics of demographic and prognostic criteria

| Therapy and observation measures                     | Mistletoe<br>group<br>(n=429) | Control<br>Group<br>(n=375) |
|--|-------------------------------|-----------------------------|
| Chemotherapy (mainly 5-FU and combinations), %       | 53.3                          | 53.9                        |
| Chemotherapy duration, mean (SD), months             | 6.1 (11.7)                    | 6.5 (12.3)                  |
| Radiotherapy, %                                      | 17.8                          | 16.5                        |
| Other supportive therapy (overall), %                | 56.7                          | 54.1                        |
| Supportive physical therapy and rehabilitation, %    | 10.5                          | 22.9                        |
| Supportive nutritional/therapeutic trace elements, % | 32.9                          | 0.8                         |
| Medicine therapy duration, mean (SD), months         | 53.4 (29.7)                   | 0                           |
| Medicine therapy, months                             | 32.9                          | 0                           |
| (0.25-133.6)   |                               |                             |
| Follow-up duration, mean (SD), months                | 61.0 (31.1)                   | 55.9 (28.3)                 |
| Median therapy, months                               | 57.8 (1-140)                  | 45.7 (1-144)                |

Table 2: Therapy and observation

## AIM OF THE STUDY

The present study was designed to evaluate the effectiveness and safety of the mistletoe product Iscador® (ISC), a fermented extract from *Viscum album L.*, administered subcutaneously 2-3 times per week as part of a long-term supportive care in patients with surgically treated UICC stage I-III primary non-metastatic colorectal carcinoma, followed by adjuvant chemo- and/or radiotherapy, or passive aftercare.

## RESULTS

### Figure 1: ADRs by adjuvant chemo- and/or radiotherapy

Among the patients actually treated with chemo- and/or radiotherapy, significantly fewer experienced ADR by the adjuvant therapy in the ISC group than in the control group (19.1% vs. 48.3%, p<0.001). The multivariable adjusted relative risk to develop such ADR during the therapy (estimated as odds ratio, OR) was significantly lower in the ISC-group compared to the control group: OR (95% CI) = 0.46 (0.28 0.77), p=0.003.

### Figure 2: Disease and therapy related symptoms

Significantly fewer patients in the ISC than in the control group showed a persistence of individual disease and therapy related symptoms adjusted for confounders after the end of therapy.

The adjusted "total symptom score" (TSS) revealed OR = 0.30, p<0.001. Among the symptoms, particularly the gastrointestinal and CNS symptoms, mucositis, as well as the TSS became consistently better in the ISC group during and after the therapy.

### Figure 3: Functional capacity assessment by Karnofsky-Index (KI)

At baseline, the KI was lower in the ISC than in the control group (mean values 77.5% vs. 85.5%), indicating a significantly worse initial general condition in the ISC group. During the therapy course, however, in the ISC group the KI improved continuously and significantly up to a mean value of 93.7% (p<0.001) at the end of therapy, while in the control group the mean value slightly decreased after the 1st therapy cycle (mean 82.4%) and returned to the baseline value (mean 84.6%) after the end of therapy; therefore no significant improvement was seen in the control group.

### Figure 4: Duration of hospitalization during therapy and follow-up

The multivariable adjusted mean (95% CI) duration of hospitalization was 35.5 (30.3-40.8) days in the ISC group as compared with 41.2 (35.8-46.6) days in the control group. Consequently, the ISC-treated patients needed on average 5.7 days less hospitalization (p=0.015) than the control group.

### Figure 5: Disease-free survival (DFS)

After multivariable adjusting for confounders by the Cox proportional hazard regression method, the relative hazard to experience a first tumor-related event (i.e. recurrence, distant metastasis, or death) during the therapy and follow-up period was significantly lower in the ISC group than in the controls. The adjusted hazard ratio HR (95% CI) = 0.68 (0.51 0.92), p=0.013, indicates a longer disease-free period and improved survival in ISC-treated patients than in controls, despite similar standard adjuvant therapy and supportive care in both groups.

## FIGURES

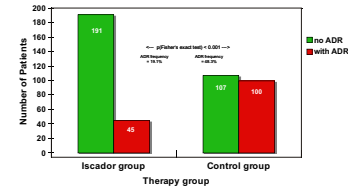


Fig. 1: Incidence of ADR associated with chemo- and/or radiotherapy. Comparison of mistletoe vs. control group.

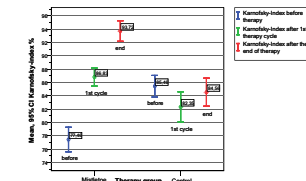


Fig. 3: Mean Karnofsky-index before, during and after the adjuvant therapy course. Comparison of the mistletoe and the control group.

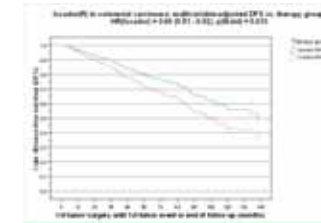


Fig. 5: Disease-free survival (DFS, multivariable-adjusted) in UICC stage I-III colorectal carcinoma patients who received supportive adjuvant mistletoe treatment (green line), compared with the control group without mistletoe (red dashed line).

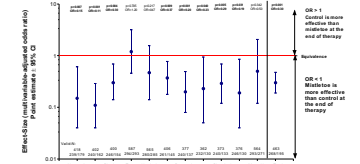


Fig. 2: Estimated risk of symptom persistence (multivariable adjusted odds ratio) in the mistletoe group compared with the control group after the end of therapy.

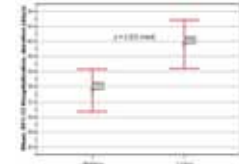


Fig. 4: Mean duration of hospitalization during the study observation period in the mistletoe treated group compared with the control group without mistletoe (descriptive analysis).

## DISCUSSION

The present study is the largest systematic comparative clinical data evaluation concerning the supportive mistletoe treatment in colorectal cancer ever performed. The results showed significantly fewer ADRs of the conventional therapy in the ISC group as compared to the control group without ISC, fewer disease- and therapy-related symptoms, and prolongation of the disease-free survival (DFS).

Despite the limitation of a non-randomized study design, the potential biases have been minimized by strict adherence to the GEP rules, unselected eligible patient data, parallel control group, systematic data quality monitoring, multivariable adjusting for baseline imbalance and confounders, and a re-confirmation of the results in sensitivity analysis.

Based on these data, a prospective randomized clinical trial to confirm these results is warranted.

## REFERENCES AND ACKNOWLEDGMENT

**References available on request at: IFAGBasel@aol.com**  
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**Corresponding author**  
 P. Heusser MD, MME, Institute of Complementary Medicine KIKOM, University of Bern, Inselspital, CH-3010 Bern, Switzerland  
 phone: +41-31 - 632 97 58, fax: +41-31 - 632 42 62,  
 email: peter.heusser@kikom.unibe.ch

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